The Seoul Journal of Medicine
Vol. 28, No. 3:219-227, September 1987

Treatment and Prognosis of High-Risk Gestational Trophoblastic Diseases[1]

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= Abstract =Based on 36 patients of high-risk gestational trophoblastic neoplasia treated with single and multiple agents chemotherapy in the Department of Obstetrics and Gynecology, Seoul National University Hospital from 1980 to 1984, the analysis of the clinical courses and therapeutic methods were carried out in order to obtain the more effective methods of treatment and improvement of the survival rate.

Chemotherapeutic agents we had used were Methotrexate, Actinomycin-D, MAC III (Methotrexate, Actinomycin-D and Cytoxan), MBP (Modified Bagshawe Protocol), and VBP (Vincristine, Bleomycin and Cis-platin) regimens.

About 60% (21 of 36) achieved complete remission after chemotherapy and adjunctive surgery: 53% (16 of 30) for metastatic disease and 83% (5 of 6) for non-metastatic disease. We could obtain two representative patterns of β-hCG regression curve in each complete and non-complete remission group from which the prognosis of the high-risk patients with gestational trophoblastic disease was anticipated.

We considered five high-risk factors significantly influencing response to treatment as follows: 1) pretreatment titer of greater than 100,000 mIU/ml serum β-hCG, 2) brain or liver metastasis, 3) trophoblastic disease after full-term pregnancy, 4) duration of disease greater than 4 months, and 5) prior unsuccessful chemotherapy. The most important factors much influencing the survival rate were 1) and 4).

Significant myelosuppression was encountered especially in the patients treated with multiple agent chemotherapy than those with single agent chemotherapy. But, the present study noted that the remission rate of high-risk patients with gestational trophoblastic disease who were treated with single agent chemotherapy was only 32%, on the other hand, remission rate of patients treated with secondary multiple agent chemotherapy was significantly increased.

We thus concluded it was very important that more aggressive primary treatment using multiple agent chemotherapy or new more effective regimen including MBP should be done to shorten the duration of treatment as early as possible depending on the regression curve and the clinical status for the high-risk patients with gestational trophoblastic disease.

Kew words: ***High-risk trophoblastic disease, Chemotherapy, Regression curve***

INTRODUCTION

Trophoblastic disease was regarded as an extremely virulent neoplasm before the original demonstration of the sensitivity to chemotherapy by Li (1956). Thereafter this neoplasm evolved into one of the most curable gynecologic malignancies with the help of hCG as a tumor marker, the identification of high-risk factors and the individualization of chemotherapy. Virtually most of patients with non-metastatic and low-risk metastatic disease are now curable. Additionally significant improvement in

[1] This study was supported in part by the clinical research grant from Seoul National University Hospital(1985).

survival for the high-risk patient began with the identification of prognostic factors and the use of primarily multiagent chemotherapy by Hammond (1973). Further improvement had resulted from the development of more aggressive therapy for patients with long-standing disease, previous chemotherapy or distant metastasis, for example, Modified Bagshawe protocol to the resistant standard triple chemotherapy of MAC (methotrexate, actinomycin-D and cytoxan).

The present study retrospectively reviewed the experience at the Department of Obstetrics and Gynecology, in Seoul National University Hospital with 36 patients who had high-risk trophoblastic disease with the respect to treatment and prognosis from 1980 to 1984.

MATERIALS AND METHODS

A review of the discharge summary chart was made for all patients from Jan. 1980 to Dec. 1984 with the diagnosis of hydatidiform-mole, invasive mole, choriocarcinoma or gestational trophoblastic disease. All pertinent records of these patients were completely reviewed to identify the patients with high-risk gestational trophoblastic disease. Thirty-six patients were identified and entered into the present study. Thirty patients were treated for chorio-carcinoma following hydatidiform-mole (11 cases, 36.7%), abortion (16 cases, 53,3%) and full term pregnancy (3 cases, 10.0%).

According to Goldstein (1982), patients with metastatic disease were classified as having high risk gestational trophoblastic disease if they had one or more of the following:

1) Pretreatment titer of greater than 100,000 mIU/ml serum beta-hCG
2) Brain or liver metastasis
3) Trophoblastic disease after full-term pregnancy
4) Duration of disease greater than 4 months.
5) Prior unsuccessful chemotherapy

The same criteria were used in this study for selection of metastatic high risk patients.

All patients were admitted and underwent investigative studies including hematology profiles, blood chemistry, chest x-ray, urinalysis and hCG determination. In addition to the items above mentioned, thyroid function tests, intravenous pyelogram, ultrasonogram, and brain computed tomography if necessary. Liver, brain and bone scan were routinely added in the cases of suggested metastasis.

Twenty-five patients were initially treated with single agent chemotherapy. In some instances, methotrexate and actinomycin-D were alternated if toxicity developed or if alternating sequential chemotherapy was used in a five day course. Courses were generally repeated after seven to eight day interval or as soon as recovery from toxicity perimitted. Combination chemotherapy including Modified Bagshawe protocol, CHAMOCA regimen and vinblastine, bleomycin, cis-platin was used in patients resistant to their first line chemotherapy and more aggressive advanced cases by clinical feature.

Chemotherapy was discontinued if the white blood cell count fell below 3,000/mm^3 or the platelet count fell below 100,000/mm^3 or severe hepatotoxicity occured. Patients with brain metastasis were confirmed by computed tomography and treated with 3000 Rads of megavoltage irradiation to the affected area over 10 days or-2 weeks period, simultaneously with chemotherapy. Hysterectomy was used in selected patients as indicated in Table 7.

Complete remission was diagnosed after 3 consecutive weekly hCG levels were within normal range and there was no clinical or radiologic evidence of disease.

RESULTS

Thirty-six of the studied patients met the criteria for high-risk gestational trophoblastic disease. Currently thirty-one patients are alive and five patients expired after chemotherapy and intensive care.

Table 1 analyzed the patients according to disease type and metastasis who received treatment at the Seoul National University Hospital between 1980 and 1984. The overall remission rate was 58%, but increased to 83% in the non-metastatic group. Four cases exhibited relapse after complete remission with multiple agents chemotherapy.

Table 2 presents the initial sites of metastasis in 36 patients. Pulmonary metastasis was the most common site; 30 of the 36 patients presented with this finding. The overall survival rate for this group was 83% (25 of 30 patients). Three of four patients who had liver metastasis are still alive The overall survival rate for those patients with brain metastasis was 75% (there of four patients). But the expired patients who had liver metastasis also had brain metastasis, so the overall survival rate for those patients with liver and/or brain metastasis was 86% (6 of 7 patients).

In the early analysis, a range of factors has been

Table 1. Results of treatments of 36 patients with high-risk gestational trophoblastic disease

Diagnosis	No. of patients	Remission (%)
Choriocarcinoma		
Metastatic	25	14 (56)
Nonmetastatic	5	4 (80)
Invasive mole		
Metastatic	1	0
Nonmetastatic	0	0
Post H-mole TRD*		
Metastatic	4	2 (50)
Nonmetastatic	1	1 (100)
Total	36	21 (58)
Metastatic	30	16 (53)
Nonmetastatic	6	5 (83)

* TRD: Trophoblastic disease.
H-mole: Hydatidiform mole

found to influence prognosis. The scoring system based on prognostic factors used in present study is summarized in Table 3. The patients detailed here are defined as patients with poor prognosis by

Table 2. Survival by sites of metastasis at initial presentation

Site of metastasis	No. of patients	Survivors	
		No	Percent
Liver	4	3	75
Brain	4	3	75
Lung	30	25	83
Vagina	4	4	100
Pelvis	0	0	
Kidney	1	1	100
Spleen	1	0	

virtue of scoring on this system if prognostic score is 7 or higher. All 36 patients in present study were regarded as patients with poor prognosis.

When patients were analyzed according to the criteria that placed them at high risk in present study (Table 4) those whose risk factor was full-term pregnancy or prior unsuccessful chemotherapy were hown to have the better survival rate than those who had other risk factors.

Patients whose disease had existed more than

Table 3. Prognostic score in gestational trophoblastic neoplasia

	0	1	2	3
A. Antecedent pregnancy	Hydatidiform mole	Nonmole abortion ectopic	Term pregnancy	
B. Interval in months between end of antecedent pregnancy and initial therapy	3	3-6	7-12	12
C. hCG value at time of initial therapy	10^3	10^3-10^4	10^4-10^5	10^5
D. ABO blood group of patient			B or AB	
E. Largest tumor (cm)	2		2-5	5
F. Site of metastases		Lung	GI tract Kidney Spleen 4-8	Brain Liver
G. Number of metastases identified		1-4	4-8	8
H. Previous chemotherapy			Failed Prophylactic chemotherapy	Failed therapeutic chemotherapy

Table 4. Survival by indication for high-risk factors

Criteria for high-risk factors	No. of patients	Survivors No.	Survivors percent
hCG ≥ 100,000 mIU/ml (S-hCG)	19	15	79
Brain and liver matastasis	7	6	86
Liver only	3	3	100
Brain only	3	2	67
Brain & liver	1	1	100
Full-term preganacy	2	2	100
Disease duration > 4 months	17	12	70
Prior unsuccessful chemotherapy	3	3	100

four months before presentation had only 70% survival rate.

Goldstein (1972) and Bagshawe (1976) described their observation on the regression pattern of hCG in trophoblastic disease patients. We were able to show similar hCG regression patterns. Two types of complete remission cases were observed, and revealed at Figure 1. More common type is that (IA) of continuous fall of hCG level through treatment course (64.7%). In remaining cases, it reveals step-ladder pattern (IB, 35.3%). This indicates stationary hCG levels for 3 weeks or 3 months with possible trophoblastic activity, but continuous fall was observed with or without chemotherapy. Two representative patterns of beta-hCG regression curve in non-complete remission group were observed. The first type (IIA) reveals a transient fall of hCG but subsequent elevation (52.6%). The second one (IIB additionally demonstrated stationary hCG level for some period but subsequent elevation (31.5%). But in three cases, the hCG curve was inadequate for regression curve due to short duration of treatment.

The toxicity concomitant with single agent and multiple combintion chemotherapy is shown in Table 5 and Table 6. In the cases of single agent chemotherapy, fourteen patients (41%) had stomatitis, nine patients (26%) thrombocytopenia and six patients (18%) hepatotoxicity. On the other hand, in the cases of multiple agent chemotherapy, toxicity is rather common, with eleven patients (44%) having neutropenia, thirteen patients (52%) throm-

Table 5. Toxicity of single agent chemotherapy in high-risk gestational trophoblastic disease

Toxicity	Regimen (affected/total No.)		Patients affected No.	Patients affected Percentage
	Act-D	MTX		
Epithelial	5/12	15/22	20/34	59
Stomatitis	3/12	11/22	14/34	41
Alopecia	1/12	1/22	2/34	6
Skin rash	1/12	3/22	4/34	23
Hematologic				
Neutropenia	1/12	1/22	2/34	6
Mild (<3,000)				
Moderate (<2,000)	1/12	1/22	2/34	6
Severe (<1,000)				
Thrombocytopenia	3/12	6/22	9/34	26
Mild (<100,000)		2/22	2/34	6
Moderate (< 75,000)		2/22	2/34	6
Severe (< 50,000)	3/12	2/22	5/34	14
Hepatotoxicity	1/12	5/22	6/34	18

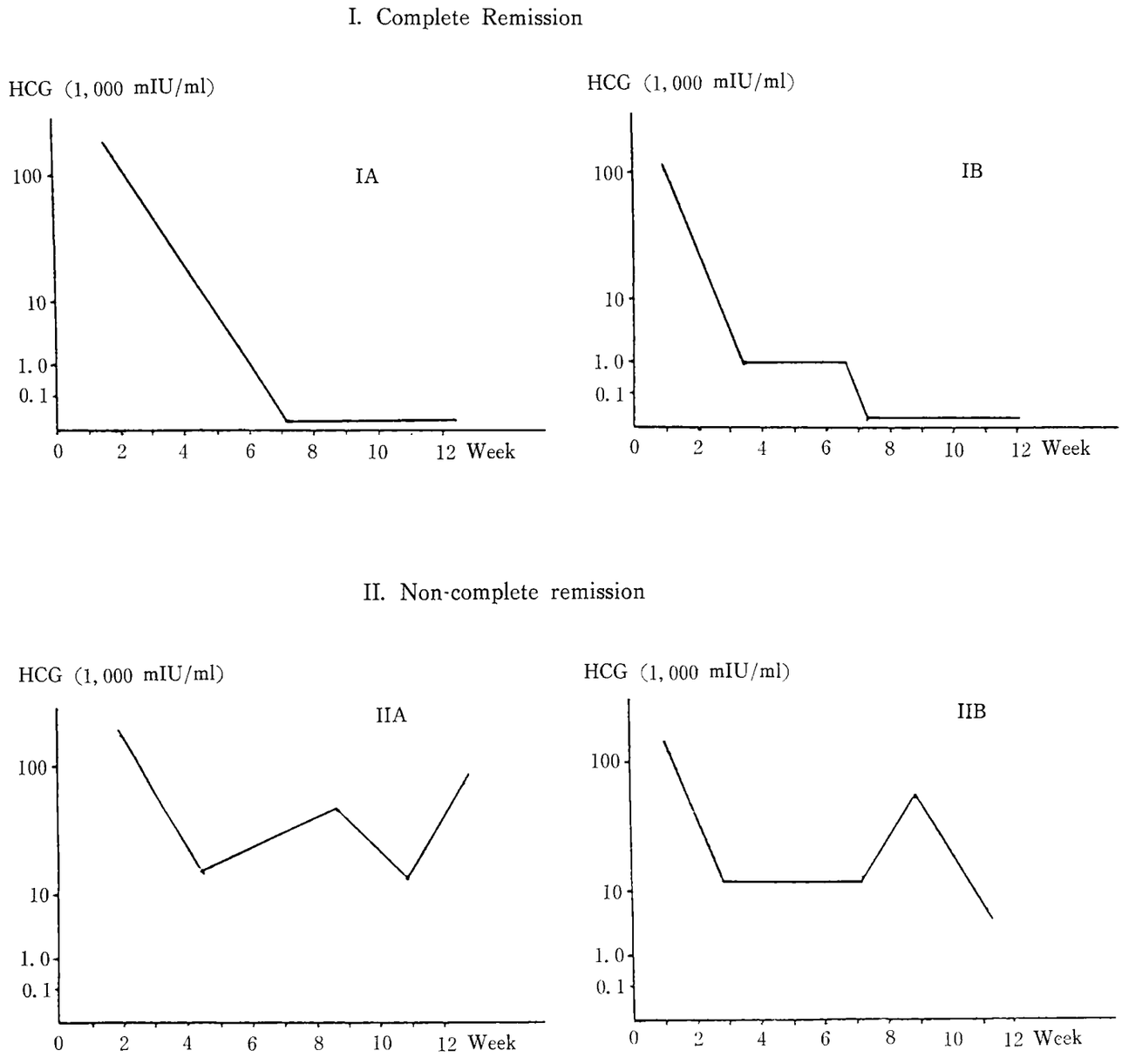

Fig. 1 HCG regression curve in high-risk gestational trophoblastic disease.

bocytopenia, and nine patients (36%) hepatotoxicity.

Surgical intervention of hysterectomy was done in seventeen patients. Details for surgical causes are revealed in Table 7. Uncontrollable vaginal bleeding, the most common cause occurred in eight of the seventeen patients (50%).

Table 8-11 reveal the response to chemotherapy in each stage. Twenty-five patients initially received single agent chemotherapy, and eight (32%) initially obained a complete remission. Nine patients were initially treated with MAC III regimen and four (44%) achieved complete remission. Nine patients were treated secondarily with MAC III regimen and five (56%) achieved complete remission.

The patients with stage I responded well to initial chemotherapy or surgery. In the patients with stage III, the response to initial single agent chemotherapy were poor, but response was relatively good to MAC III regimen or surgery. In the patients with stage IV, the response was very poor to single or multiple agent chemotherapy except MBP, VBP or surgery.

Table 6. Toxicity of multiagent chemotherapy in high-risk gestational trophoblastic disease

Toxicity	Regimen (affected/total No.)		No. of affected patients	Percentage
	MAC	CHAMOCA		
Epithelial				
Stomatitis	7/20	3/5	10/25	40
Alopecia	10/20	4/5	14/25	56
Skin rash	4/20	2/5	6/25	24
Hematologic				
Neutropenia	7/20	4/5	11/25	44
Mild	2/20	3/5	5/25	20
Moderate	3/20		3/25	12
Severe	2/20	1/5	3/25	12
Thrombocytopenia	12/20	1/5	13/25	52
Mild	3/20	1/5	4/25	16
Moderate	4/20		4/25	16
Severe	5/20		5/25	20
Hepatotoxicity	8/20	1/5	9/25	36
Eye irritation		2/5	2/25	8

* MAC = Methotrexate, Actinomycin-D, Cytoxan

Table 7. Reasons for hysterectomy in high-risk gestational trophoblastic disease

Reasons	No. of patients
Uterine rupture	2
Massive or prolonged vaginal bleeding	8
Huge abdominal mass	1
Resistance to chemotherapy	5
Biopsy proven localized mass	1
Total	17

DISCUSSION

The overall remission rate of 58% in the present study is rather lower than those shown by others (Bagshawe 1976, Gordon *et al.* 1985). Patients who were diagnosed early and treated vigorously could expect a 90% remission rate, even with metastasis, but patients seen later with extensive disease had only a 36% chance of recovery. This success is the consequence of the recognition of patients at high risk for failure of treatment and individualization of therapy so that high risk patients are treated aggressively with combination

Table 8. Therapeutic modality (single or multiple agent chemotherapy) for high-risk gestational trophoblastic disease

Treatment category	No. of patients		No. of remission (%)	
	1°	2°	1°	2°
Single agent	25	0	8(32)	0
Multiple agent				
MAC III	9	9	4(44)	5(56)
CHAMOCA	1	1	1(100)	0
MBP	1	2	0	2(100)
VB	0	1	0	1(100)
VBP	0	1	0	1(100)

Table 9. The response to chemotherapy and surgery in stage I

Remission therapy	Remission/Total No.of patients		
	H-mole	Inv.-mole	CCA*
Initial			
MTX	1/1	—	4/4
Act-D	—	—	—
Hysterectomy	1/1	—	3/3
Resistant			
MAC III	—	—	0/1
Hysterectomy	—	—	0/1

* CCA: Choriocarcinoma
H-mole: Hydatidiform mole status

Table 10. The response to chemotherapy and surgery in stage III

Remission therapy	Remission/Total No.of patients		
	H-mole	Inv.-mole	CCA*
Initial			
MTX	0/3	—	0/10
Act-D	—	—	0/2
MAC III	0/1	0/1	4/5
Hysterectomy	—	—	6/7
Resistant			
MAC III	2/3	—	4/6
MBP	—	—	1/1
CHAMOCA	—	—	0/1
Hysterectomy	—	—	2/3

* CCA: Choriocrcinoma
Inv. mole: Invasive mole

Table 11. The response to chemotherapy and surgery in stage IV

Remission therapy	Remission/Total No.of patients		
	H-mole	Inv.-mole	CCA*
Initial			
MTX	—	—	0/4
Act-D	—	—	0/1
MAC III	—	—	0/1
CHAMOCA	—	—	0/1
MBP	—	—	0/1
Resistant			
MAC III	—	—	0/2
MBP	—	—	2/2
VB	—	—	0/1
VBP	—	—	1/1
Hysterectomy	—	—	1/1

* CCA: Choriocarcinoma
MAC: Methotrexate, Actinomycin-D, Cytoxan
MBP: Modified Bagshawe Protocol
VB : Vinblastine, Bleomycin
VBP: Vinblastine, Bleomycin, Cis-platin

chemotherapy with or without adjuvant radiation.

Complete remission from metastatic gestational trophoblastic disease was achieved by Hertz *et al.* (1961) in 47% of the patients with methotrexate alone and in 74% of the patients with both methotrexate and actinomycin-D sequential therapy. But overall remission from the metastatic group was achieved in 60% of patients with single and triple chemotherapy. In the present series, this was only 41% in high-risk metastatic gestational trophoblastic disease patients with single and multiple chemotherapy. Possible explanation for the above data was that of less frequent methotrexate and actinomycin-D sequential chemotherapy.

Factors found to be significant in determining prognosis and therefore in categorizing as a high-risk patients were follows:

1) Cinicopathologic diagnosis of choriocarcinoma
2) Duration more than 4 months from antecedent pregnancy event in treatment.
3) Pretreatment hCG titer greater than 100,000 mIU/ml
4) Metastasis to sites other than lung and vagina
5) Antecedent term pregnancy.

Jones and Lewis (1974) failed to show an effect of histopathologic diagnosis on survival. On the other hand, Brewer and collegues (1982) and Goldstein (1972) reported poor prognosis in patients with a histologic diagnosis of choriocarcinoma. In the present study, only a slight influence is noted as revealed in Table 1.

Present study reports that the thirteen patients with less than 4 months between antecedent pregnancy and treatment are still alive. These results demonstrate that time from antecedent pregnancy event was a significant influencing factor of response to therapy in patients with metastatic gestational trophoblastic disease. But Smith (1975) and Lewis (1961) could not demonstrate any correlation between duration of disease and response to treatment. In the present series, choriocarcinoma patients generally had higher hCG titer than did patients with invasive moles.

Nineteen patients (63%) had pretreatment hCG titers greater than 100,000 mIU/ml. Ross and col-

leagues (1973) found significantly higher remission rates among 50 patients with metastatic (1976) disease with hCG titers less than 100,000 mIU/ml (serum beta-hCG). Bagshawe (1976) also found that both hCG titer and disease duration had an important influence on survival.

Hertz and colleagues (1956) demonstrated a poor prognosis in patients with brain metastasis and a site of metastasis known to affect survival. In the present series, pulmonary metastasis is the most common site. Survival was 83% when pulmonary metastases present, but it fell to lower level when metastasis were present at sites other than the lung and vagina. Although present reported cases are too few to draw significant conclusions, but liver and/or brain metastasis are important factor for prognosis.

Surwit (1984) and Hammond (1973) reported that among a group of high-risk patients, preceding pregnancy was not a significant factor in patients with other high-risk criteria. Patients in this series who presented after a full-term pregnancy showed remission after chemotherapy, even though one of them had a high hCG value.

In Surwit (1984) and Hammond's (1973) series, 50% of 17 patients who had received prior chemotherapy entered remission, whereas remission occurred in 82% of 34 high-risk patients treated primarily at their center.

A range of factors has been found to influence prognosis. It is unlikely that all the prognostic factors are independent variables, but the data available for analysis are complicated by the changing pattern of chemotherapy in the past quarter century. The scoring system (Goldstein, 1982) used in our study is summaried in Table 3. All the patients employed in the present studies were defined as poor prognosis cases by virtue of scoring on this system.

Goldstein (1972) and Bagshawe (1976) reported their observation on the regression pattern of hCG in postmolar patients. Three types of regression pattern were observed by Wong (1982). In this study, we are able to make similar observations in 36 patients with high-risk factors. We observed this similar pattern in the remission group, and the other two patterns in non-remission group. From our observation, patients showing non-remission hCG regression pattern should be treated more aggressively with combination chemotherapy or new drugs.

Chemotherapy remains the primary method of treatment for gestational trophoblastic neoplasia, and better remission rates can partly be attributed to the advent of multiagent chemotherapy. Earlier workers reported that surgery was useful only to remove the known focus of disease, either primarily or secondarily after only partial response to chemotherapy, to control hemorrhage, to relieve obstruction, to treat infection, or to deal with other life threatening complications so that the patient could survive and ultimately be cured by chemotherapy. The present study also supported these observations. Ten patients, (63%) of this group revealed remission, quite higher than that of all studied patients. This suggest that hysterectomy was possibly helpful for disease regression.

Of high risk metastatic gestational trophoblastic disease patients primarily treated with methotrexate, actinomycin-D, cytoxan 63% (20 of 32) achieved complete remission by Gordon (1985). Although remission is noted in only one case, new effective chemotherapy, including vinblastine, bleomycin and cisplatin, needs to be developed for common use in high-risk patients. Finally the management of high risk gestational trophoblastic disease demands the use of intensive and often toxic chemotherapy.

In the present study, we confirmed initial single agent chemotherapy only is inadequate and early incorporation of the multiple agent chemotherapy is recommended for resistant disease.

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= 국문초록 =

Treatment and Prognosis of High-Risk Gestational Trophoblastic Diseases

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최근 보고 등에 의하면 비전이성 융모상피종은 수술여부와 관계없이 거의 100% 약물요법으로 치료가능하며 전이성 환자의 경우는 고위험군이 저위험군에 비해 관해율이 분명히 떨어짐을 보여주고 있다. 따라서 고위험군 환자의 전반적 임상소견과 치료방법 및 그 성적에 대한 분석을 철저히 함으로써 앞으로 이들 환자의 치료 및 생존율을 향상시키는데 크게 도움이 되리라 생각한다. 이에 저자들은 1980년 1월부터 1984년 12월 사이 5년간 서울대학교 병원 산부인과에서 화학요법 및 수술을 시행하였던 융모상피종 환자 36명을 대상으로 연구분석 하였다.

환자의 연령은 21-30세가 17명 (45%)으로 가장 많았으며 병기별 분포로는 제3기가 22명 (58%)으로 가장 많았다. 화학요법은 Methotrexate, Actinomycin-D, MAC III regimen, CHAMOCA regimen, MBP regimen 및 VBP regimen 등을 사용하였다.

* MAC III: Methotrexate, Actinomycin-D 및 Cytoxan
* MBP: Modified Bagshawe Protocol
* BVP: Vinblastine, Bleomycin 및 Cis-platin

약 60% (36명중 21명)에서 화학요법 및 보조적 수술요법으로 완전 관해 (complete remission)를 보였으며 전이성 융모상피종의 경우에는 53% (30명중 16명), 비전이성 융모상피종의 경우에는 83% (6명중 5명)로 나타났고, 보조적 수술요법을 받은 환자군이 그렇지 않은 환자군에 비해 관해율이 다소 높게 나타났다.

혈청 β-hCG 치의 회귀곡선 (regression curve)은 관해 및 비관해군에서 각각 특징적인 2가지 곡선을 얻을수가 있었으며, 고위험군 인자중 혈청 β-hCG 측정치가 10만 이상인 경우와 선행임신부터 초회치료간 기간이 4개월 이상인 경우에서 가장 낮은 생존율을 보였다.

화학요법의 경우 그 부작용의 발생은 복합요법의 경우가 단일 화학요법의 경우보다 대체적으로 2-7배의 빈도로 많았으며, 특히 과립적혈구의 감소가 가장 두드러지게 나타났다.

고위험군 융모상피종 환자에서의 단일 화학요법으로는 관해율이 32%에 불과한 반면 2차적으로 복합약물요법을 사용한 경우 관해율이 현저히 증가되는것을 발견할 수 있었다.

따라서 고위험군 융모상피종 환자는 회귀곡선 및 임상적 판단에 따라 빠른시간내에 집중적이고 효과적인 복합요법을 시작함으로써 불필요하게 치료기간이 지연되는 것을 막는것이 매우 중요하다는 결론을 얻었다.